DETAILED ACTION

1. This action is in response to the reply of August 28, 2009. Applicant's arguments and amendments to the claims have been fully considered but are not persuasive to place all claims in condition for allowance. All rejections not reiterated herein are hereby withdrawn. In particular, the rejection of claims 1, 3, 6 and 7 under 35 USC 112, first paragraph, written description (new matter) has been obviated by the amendments to the claims.

2. Claims 1, 3, 6, 7 and 15 are pending.

Claims 1, 3, 6 and 7 have been examined herein. Claim 1 has been examined only to the extent that the claim reads on the elected methods which detect a genotype of K8 by assaying nucleic acids for the K8 R340H mutation. The non-elected subject matter of methods which assay for a mutation in a protein and which assay for the additionally recited non-elected mutations are withdrawn from consideration as being drawn to a non-elected invention.

Claim 15 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on May 29, 2008. Note that claim 15 encompasses the detection of non-elected mutations from Invention I and II. In view of the fact that claim 3, from which claim 15 depends, is not allowable, the method of claim 15 which detects K8 and K18 mutations in addition to the elected R340H K8 mutation, constitutes a non-elected invention. Applicants should also note that claim 15 recites detecting genotype change relative to

SEQ ID NO: 4, wherein the genotype change is selected from the recited K8 and K18 amino acid changes. However, SEQ ID NO: 4 is limited to the K8 amino acid sequence, as opposed to a K18 amino acid sequence.

Declaration under 37 CFR 1.132

3. The declaration under 37 CFR 1.132 filed August 28, 2009 is insufficient to overcome the rejection of claim 1 based upon 35 USC 112, first paragraph as set forth in the last Office action for the reasons discussed in paragraph 6 detail below.

Claim Objections

4. Claim 1 is objected to because the claim includes subject matter of the non-elected inventions, namely the detection of the mutations other than K8 R340X and methods which assay for a mutation in a protein.

Response to Remarks:

In the response, Applicants state that claim 1 has not been further limited "in view of the previous species election, as the claim shall be restricted to this species if no generic claim is finally held allowable."

Applicant's response has been fully considered. However, no claims are pending which are generic and in particular claim 1 is not a generic claim - e.g., a claim to a method which detects any mutation in the K8 gene. Rather, claim 1 recites specific mutations that are structurally and functionally distinct one another. As the mutations do not share both a common structure and function, they are not of a similar nature and do not share a corresponding technical feature. As indicated in the restriction requirement of March 19, 2008, the non-elected mutations would only be considered for rejoinder

with the elected K8 R340H mutation upon the allowance of a generic claim.

Additionally, claim 1 includes the non-elected subject matter of Invention II, directed to methods of detecting a predisposition to liver disease by assaying for mutation in a **K18** nucleic acid. The elected invention of Group I is limited to methods which assay for a mutation in a **K8** nucleic acid.

New Grounds of Rejections Necessitated by Applicant's Amendments to the Claims

Claim Rejections - 35 USC § 112 second paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 6 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3, 6 and 7 are indefinite over the recitation of "analyzing nucleic acid of an individual human for a change in genotype relative to a SEQ ID NO: 4 codon 340." SEQ ID NO: 4 is the amino acid sequence of the K8 protein. Thereby, it is unclear as to what is intended to be encompassed by analyzing a nucleic acid for a genotype of an amino acid sequence or what is meant by a nucleic acid genotype relative to codon 340 of an amino acid sequence.

Maintained Rejection

Claim Rejections - 35 USC § 112 - Enablement

6. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for identifying a human subject at increased risk for viral hepatitis or acute fulminant hepatitis (AFH) comprising: (a) providing a nucleic acid sample from said human subject wherein the nucleic acid sample comprises a nucleic acid encoding keratin 8; (b) analyzing the sequence of the nucleic acid encoding keratin K8 to determine the identity of the nucleotides encoding codon 340; and (c) determining that said human subject has an increased risk for viral hepatitis or AFH if said human subject has the sequence CAT at codon 340 of the nucleic acid encoding keratin 8 as compared to a human subject that has the sequence CGT at codon 340 of the nucleic acid encoding keratin 8, does not reasonably provide enablement for methods for determining a predisposition to any noncryptogenic liver disease by determining a mutation in the keratin 8 gene resulting in a R340H substitution. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection was previously presented in the Office action of August 10, 2009 and is maintained for the reasons set forth therein.

Response to Remarks:

In the response, Applicants traversed this rejection.

Applicants further provided a 132 Declaration by the present inventor including the content of the article filed on April 29, 20009 that has been submitted to the New England Journal of Medicine. The declaration states that " We found that KRT8/KRT18

are important susceptibility genes for ALF development. The presence of K8/K18 variants predisposes to an adverse acute liver failure (ALF) outcome." It is also stated that "Acute liver failure (ALF) involves ~2000 US cases/year and is characterized by sudden loss of hepatocyte function in previously liver-healthy subjects that may lead to profound morbidity and mortality. Drug-induced liver toxicity is the most common cause of adult ALF mainly because of acetaminophen (APAP) poisoning (-1/2 of US ALF cases). Other frequent ALF etiologies include hepatitis B (7%), indeterminate (14%), autoimmune (5%) and drugs other than APAP (11%)."

The 132 Declaration has been fully considered but is not sufficient to overcome the present grounds of rejection. All data provided in the 132 Declaration is directed to an association between K8 or K18 mutations and **acute liver failure**. The present claims are not, however, limited to methods for detecting a predisposition to acute liver disease. Rather, the present claims are directed to a method which detects a predisposition to all noncryptogenic liver diseases. Yet, the 132 declaration does not provide any information regarding an association between the disclosed K8 or K18 mutations, and particularly the elected R340H K8 mutation, and other types of noncryptogenic liver disease. Neither the 132 declaration or the response provide any arguments or evidence to establish that the findings obtained with acute liver failure can be extrapolated to the genus of noncryptogenic liver diseases. The present claims encompass a significantly large genus of noncryptogenic liver diseases that differ from one another with respect to their etiology and symptoms. There is nothing of record to indicate that the results obtained with acute liver failure, viral hepatitis or acute fulminant

hepatitis can be extrapolated to the genus of noncryptogenic liver diseases. For example, it remains unclear as to how the association between the R340H mutation and acute liver failure results in the conclusion that the mutation causes or is otherwise indicative of a predisposition to developing liver cancer, for instance, given the distinct underlying molecular processes associated with acute liver failure as compared to liver cancer. It is also noted that the specification as originally filed does not appear to provide basis for the subgenus of liver diseases characterized by acute liver failure.

Additionally, it is noted that the findings presented in the 132 Declaration are directed to the **R341H** K8 mutation. Neither the declaration nor the response clearly indicate the relationship between the R341H K8 mutation and the elected R340H K8 mutation.

The response states that the mutations in K8 have an “underlying molecular logic, ” such as the destablization of a protein. Applicants point to the teachings of Ku et al (2002. Gastroenterology) as stating that there is an "extensive body of transgenic animal data showing that keratins play an essential role in protecting hepatocytes from mechanical and nonmechanical stresses.” However, the Ku et al paper constitutes Applicants own work. It is not considered to be impartial in nature and thereby cannot be relied upon to establish enablement of the claimed invention. Additionally, the response does not establish that the R340H mutation alters the functional activity of keratin K8 in a manner that effects hepatocytes from mechanical and nonmechanical stresses, as would be necessary to support the contention that this mutation is associated with noncryptogenic liver diseases in general.

The response points to Table 6 (page 27 of the specification) as teaching the molecular consequences of the keratin mutations. This table indicates that the R340H mutation has the "potential effects" of destabilization. The table does not indicate what is destabilized. Further, while the table lists the potential effect, the table and specification do not in fact establish or provide any type of evidence to show that the mutation in fact has this effect. Most importantly, the specification and response do not explain why this potential effect of destabilization would be expected to cause or otherwise be associated with a representative number of noncryptogenic liver diseases.

Applicants assert that K8 R340H has been shown to be a mutation hot spot. However, the specification and response do not explain why or provide any type of evidence to support an assertion that a mutation hot spot would necessarily be correlated with all types of noncryptogenic liver diseases or other types of liver disease.

The response asserts that the claims meet the enablement requirement because the specification teaches how to determine the sequence of a polynucleotide and that this requires only routine experimentation. This argument is not persuasive because the claims are not directed to general methods for determining the nucleotide sequence of a K8 polynucleotide. Rather, the claims are directed to methods for determining a predisposition to any particular or to all non-cryptogenic liver diseases. Further, it is maintained that the experimentation is undue because the results of such experimentation are highly unpredictable, for the reasons discussed in detail above. For example, Ku (May 2001) was cited in the above rejection as teaching that while the Gly61Cys and Tyr53His mutations were detected in patients having cryptogenic

cirrhosis, these mutations were not detected “in the patients with other liver diseases” (see abstract). The "other liver diseases” in which the mutations were not present include hepatitis C, autoimmune hepatitis, acute fulminant hepatitis, primary bilary cirrhosis, Wilson’s disease, hepatitis B and neonatal hepatitis (page 1581, para 1). The response does not specifically address this reference or this aspect of the rejection.

Applicants state that there may be some non-functional variants within the genus defined by the claims, but assert that Applicants are not required to establish that every species within a claimed genus will work. This argument has also been fully considered but is not persuasive. While Applicants are not required to establish that all species encompassed by the claims are operable, Applicants are required to establish the enablement of a representative number of species encompassed by the claims. In the present situation, Applicants have established an association only between the CGT to CAT mutation at the codon encoding position 340 of the K8 protein and the risk of viral hepatitis and acute fulminant hepatitis in human subjects. Establishing the enablement of 2 species (viral hepatitis and AFH) within a genus of thousands of possible species (i.e., any non-cryptogenic liver disease, including e.g., Wilson’s disease, cystic fibrosis, primary oxalosis, Nieman-Pick, any liver cancer, any polycystic disease, carcinoid, biliary atresia, autoimmune hepatitis, neonatal hepatitis, etc) is not considered to be sufficient to establish the enablement of a representative number of species within the broadly claimed genus.

The response states that the invention is not based only on association studies but is also based on animal models. However, the response does not point to any

particular teachings in the specification of an animal model that establishes that the CGT to CAT mutation encoding codon 340 keratin K8 is associated with a representative number of distinct kinds of noncryptogenic liver diseases in human subjects.

The response cites the Board decision of Ex parte Xu et al as "relevant to the facts of the present application." The response does not state how this decision is relevant to the facts of the present application.

The Ex parte Xu decision in fact is limited to a finding regarding the enablement of a claim to a method for screening for increased risk of prostate cancer by assaying for the presents of the R293X and D174Y mutations in the MSR1 based on the teachings in the specification therein of a relationship between the R293X and D174Y mutations. The fact pattern of the application upon which this decision was rendered are distinct from the present situation. In the cited decision, the BPAI noted that "increased risk" indicated that there is only an increased possibility or probability of getting prostate cancer. The BPAI also noted that the specification had provided evidence of that the R293X and D174Y mutations were detected in several families with familial and hereditary prostate cancer. This is in contrast to the present specification which teaches only an association between the CGT to CAT mutation encoding codon 340 keratin K8 and viral hepatitis and acute fulminant hepatitis, but does not teach an associated between this mutation and a representative number of other distinct kinds of noncryptogenic liver diseases or an association with noncryptogenic liver disease in general. It is also noted that the genus of "prostate cancer" includes sporadic and

hereditary prostate cancer, and that these two types of cancer are significantly related with respect to their biological attributes. This is distinct from the present situation wherein the claimed genus of noncryptogenic liver diseases includes a significantly large number of diverse diseases which differ from one another with respect to their etiology and symptoms. It has not been established that the R340H mutation has a common functional effect or role in the occurrence of a representative number of noncryptogenic liver diseases.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is 571-272-0747. The examiner can normally be reached on Monday-Thursday (6:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on 571-272-07630763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Carla Myers/

Primary Examiner, Art Unit 1634